EVIDENCE ON THE DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF METRIBUZIN

REPRODUCTIVE AND CANCER HAZARD ASSESSMENT SECTION
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Metribuzin

- Asymmetrical triazine herbicide (MW 214.3 D)
- Used as herbicide on agricultural crops, ornamentals, and landscape maintenance
- Slightly soluble in water
- Somewhat soluble in organic solvents

Pharmacokinetics

- Fairly rapidly absorbed orally
- Numerous metabolites
- Distributes to all organs examined
- High concentrations in thyroid, liver, kidney
- Low concentrations in testes and ovaries
- No data on placenta or fetus
- Excreted in urine and feces

Non-DART toxicities

- Acute oral LD_{50}s vary: 245 mg/kg in male guinea pig to 2,200 mg/kg in male Wistar rat
- Subchronic and chronic toxicity typically reduced body weight or weight gain, increased liver weight
- Complex effects on thyroid function: altered T4 levels, histopathology
- Transient neurobehavioral effects

Studies with data relevant to developmental toxicity

- No human data
- Two rat developmental studies (Bayer 1972, Miles 1986)
- Two rabbit developmental studies (MRI 1981, Miles 1989, 1991)
- Two rat reproductive studies (Bayer 1974a, Miles 1988, 1990)

FB 30 rat developmental study (Bayer 1972)

- Mated rats treated at 0, 5, 15, 50 or 100 mg/kg/d by gavage on gd 6-15, sacrificed on gd 20

Effects observed:

- No developmental toxicity
- Slight, non-statistically significant reduction in maternal weight gain at the high dose

Sprague-Dawley rat developmental study (Miles 1986)

- Mated rats treated at 0, 25, 70 or 200 mg/kg/d by gavage on gd 6-15, sacrificed on gds 16 & 20

Effects observed:

- Reduced fetal weight at low, middle, and high doses
- Delayed fetal ossification, increased wavy, curved, or bulbous ribs at high dose
- Reduced maternal food consumption, lower body weight, reduced weight gain at low, middle, and high doses

New Zealand White rabbit developmental study (MRI 1981)

- Mated rabbits treated at 0, 15, 45 or 135 mg/kg/d by gavage on gd 6-18, sacrificed on gd 30

Effects observed:

- Increased abortions and early resorptions, reduced fetal weight, increased incompletely ossified sternebrae (none statistically significant) at high dose
- Slightly reduced fetal weight at middle dose (not statistically significant)
- Maternal weight loss during treatment at high dose (statistically significant)

American Dutch rabbit developmental study (Miles 1989, 1991)

- Mated rabbits treated at 0, 10, 30, or 85 mg/kg/d by gavage on gd 6-18, sacrificed on gd 28

Effects observed:

- Reduced fetal weight and delayed ossification in middle dose group, but not high dose group
- Reduced maternal weight gain at high dose

FB30 rat reproductive study (Bayer 1974a)

- Male and female rats treated at 0, 35, 100, 300 ppm in food for 3 generations with 2 litters/generation

Effects observed:

- Birth weights generally lower than controls in F2 and F3 generations (not statistically significant)
- No parental toxicity

Sprague-Dawley rat reproductive study (Miles 1988, 1990)

- Male and female rats treated at 0, 30, 150, or 750 ppm in food for 2 generations with 1 litter/generation

Effects observed:

- Reduced implantations and litter size in F1/F2 litter at middle and high concentrations
- Reduced maternal weight at high concentration in F0, and middle and high concentrations in F1

Studies with data relevant to female reproductive toxicity

- No human data
- Two rat reproductive studies
  (Bayer 1974a, Miles 1988, 1990)
- Mouse female dominant lethal study
  (Bayer 1974c)
- Several subchronic and chronic studies in mouse, rat, rabbit, dog

Rat reproductive studies

- Effects observed same as previously described under developmental
- No consistent effects on fertility, other reproductive endpoints

Female mouse dominant lethal study (Bayer 1974c)

- Female NMRI mice treated by gavage in proestrus at 0 or 300 mg/kg, mated with untreated males, sacrificed on gd 14

Effects observed:

- No dominant lethal or other adverse reproductive effects
- Mild maternal drowsiness

Subchronic and chronic studies: female

- Most studies found no effect on ovarian weight, gross pathology or histopathology
- One inhalation study and one oral study in rats found increased relative ovary weight, no effect on absolute ovary weight, in presence of reduced body weight
- A chronic study in dogs found reduced absolute and relative ovary weight at a severely systemically toxic concentration (3/4 animals died, etc.)

Studies with data relevant to male reproductive toxicity

- No human data
- Two rat reproductive studies
  (Bayer 1974a, Miles 1988, 1990)
- Two male mouse dominant lethal studies
  (Bayer 1975, 1976)
- Several subchronic and chronic studies in mice, rats, rabbits, dogs

Rat reproductive studies

- Effects as described under developmental toxicity
- No consistent effects on fertility, or other reproductive endpoints

Male mouse dominant lethal studies (Bayer 1975, 1976)

- Male NMRI mice treated once at 0 or 300 mg/kg, mated with untreated females for one-week periods for 8 periods (Bayer 1975) or four-day periods for 5 periods (Bayer 1976). Females sacrificed on gd 14

Effects observed:

- No consistent dominant lethal or other reproductive effects
- Mild paternal drowsiness

Subchronic and chronic studies: male

- Most studies found no effect on testes weight, gross pathology or histopathology
- Two inhalation studies in rats found increased relative testes weight, no effect on absolute testes weight, in presence of reduced body weight
- A chronic study in dogs found reduced absolute but not relative testes weight and “immature” testes at a severely systemically toxic concentration (3/4 animals died, etc.)

Summary: developmental

- Sprague-Dawley rat developmental study
  Reduced fetal weight all doses, delayed ossification and rib anomalies at high dose
  Reduced maternal food consumption, lower body weight, and reduced weight gain at all doses
- Sprague-Dawley rat reproductive study
  Reduced implantations and litter size in F1/F2 at middle and high concentrations
  Reduced maternal weight in F0 at high concentration and F1 at middle and high concentrations
- New Zealand White rabbit developmental study
  Increased abortions, resorptions, and incompletely ossified sternebrae, reduced fetal weight at high dose (not SS)
  Maternal weight loss at high dose

Summary: female reproductive

- Sprague-Dawley rat reproductive study
  Reduced implantations & litter size in F1/F2 at middle and high concentrations
  Reduced maternal weight in F0 at high concentration and F1 at middle and high concentrations
- Two rat subchronic studies
  Increased relative but not absolute ovary weight
  Reduced body weight
- Dog chronic study
  Reduced absolute and relative ovary weight
  Severe systemic toxicity (3/4 dead, etc.)

Summary: male reproductive

- Sprague-Dawley rat reproductive study
  Reduced implantations & litter size in F1/F2 at middle and high concentrations
  Reduced maternal weight in F0 at high concentration and F1 at middle and high concentrations
- Two rat subchronic studies
  Increased relative but not absolute testes weight
  Reduced body weight
- Dog chronic study
  Reduced absolute testes weight, “immature” testes
  Severe systemic toxicity (3/4 dead, etc.)